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FROMMER LAWRENCE & HAUG
745 FIFTH AVENUE- 10TH FL.
NEW YORK, NY 10151

EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/623,611	COIA ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32 and 34-41* is/are pending in the application.

4a) Of the above claim(s) *22-27 and 29-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21, 28, 34-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1644.

Applicant's amendment, filed 1/29/04, has been entered.
Claims 1-32 have been amended.
Claim 33 has been canceled.
Claims 34-41 have been added.

Applicant's request for rejoinder of claims 22-32 for the reasons discussed below is acknowledged. However, it is unclear which reasons are being relied upon for rejoinder. In addition, prosecution of the claims under consideration with respect to the elected invention is maintained for the reasons of record and set forth herein.

As pointed out previously, applicant's election with traverse of Group I and species elections of somatostatin, human antibodies, and V86 in Paper No. 20 was acknowledged. The traversal was on the grounds that unity of invention exists because Group I does define a contribution over the prior art. This is not found persuasive for the reasons provided in detail in the discussion of Applicant's comments with respect to Peach et al. in the rejection set forth under 35 USC 102.

The requirement was still deemed proper and was therefore made FINAL.

Claims 22-27 and 29-32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 20.

Claims 1-21, 28 and 34-41 *are under consideration in the instant application.*

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Action will be in response to applicant's arguments, filed 1/29/04.
The rejections of record can be found in previous Office Action, mailed 7/28/03.

Claim Rejections - 35 USC § 112 second paragraph

3. Claims 1-10, 13-21, 28, 34-37 and 40-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-10, 13-21, 28, 34-37 and 40-41 are ambiguous in their recitation, either directly or via their dependency, of a "V-like domain (VLD) derived from a non-antibody ligand".

It is acknowledged that the specification on page 5 at lines 25-30 disclose that a VLD is a domain which has structural features *similar to* the variable heavy or variable light domains of an antibody, including the CDR loop structures, but is neither an antibody nor a TcR. However, the metes and bounds of this limitation are unclear at least in that Table 1 on page 6 indicates that VLD derived from non-antibody ligands includes proteins which have a "C domain" but not a "V domain" (e.g., CD16 and CD19 in Table 1). Thus it is unclear if the term "VLD" is limited to only those domains considered to be "V domains" in the art, or if it also encompasses any domain that might be broadly construed to be a "V-like domain" by some undefined criteria.

Applicant's arguments in conjunction with the Exhibits, filed 1/29/04, have been fully considered but are not found convincing essentially for the reasons of record.

Applicant relies upon the definition of "V-like domain" on page 5 of the instant specification as one which has "similar structural features to the variable heavy or variable light domains of an antibody" and provides examples of suitable non-antibody ligands which *may* provide V-like domains suitable for the invention.

Applicant's reliance on the Leucocyte Facts Book (1993) Eds. Barclay et al., Academic Press, London (Barclay) to analyze the definiteness of the claim language.

In response to applicant's reliance on the incorporation by reference of Barclay in the specification as filed, applicant is reminded that to incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where the material is found in the various documents. See Advanced Display Systems, Inc. v. Kent State Univ., 54 USPQ2d 1673 (Fed. Cir. 2000) citing In re Seversky, 177 USPQ 144, 146 (CCPA 1973).

Page 6 of the specification as filed discloses that the Non-Antibody Ligands listed in Table 1 are discussed in Barclay. However, the specification as filed does not provide direction to the definition of "V-like domain" or the characteristics relied upon by applicant to define the characteristics of said "V-like domain".

Further, it appears that applicant relies upon the requirement of the combination of structural similarity and sequence similarity as defined through computer analysis, as indicated by Barclay. However, such analysis, including those structural or sequence parameters are not supported by the instant specification as filed.

Although there may be a common topology of fold that is achieved by different sequences with respect to immunoglobulin-like domains, Bork et al. (J. Mol. Biol. 242: 309-320(1994) disclose that no single interaction or localized set of interactions can be uniquely identified as a principal determinant of the immunoglobulin-like fold, given the extreme sequence diversity (see page 318, column 2, paragraph 2). The variety of features observed in the different immunoglobulin-like domain would lead to the expectation that further subtypes and modifications of the topology (see page 318, column 2, paragraph 4). In addition, even within a one protein the different structurally similar domains have distinct binding functions (see page 318, column 1, paragraph 2). The determined crystal sturctures also reveal different binding modes, apparently each part of the surface of the domain can be used for interaction with other molecules (page 318, column 1, paragraph 1).

While applicant relies upon the extensive use of "V-like extracellular domain" and "V-like domain" with reference to CD28 and CTLA-4 in the Peach et al. reference of record, it is noted that the claims are not limited to CD28 and CTLA-4. In addition, applicant relies upon the usage of "V-like domain" in the context of certain molecules such as CD22, however the claims are not limited to known molecules with known "V-like domains".

While applicant relies, in part, on several on-line resources for providing structural information with respect to sequence and structures of immunoglobulins and immunoglobulin-like molecules, this information does not appear to provide a clear understanding of the metes and bounds of "V-like domain" at the time the invention was made, as acknowledged by applicant.

Also, it appears that applicant is relying upon these references to establish certain criteria to distinguish "V-like domains" from other Immunoglobulin superfamily members, however such distinctions do not appear in the specification as filed.

Applicant's arguments are not found persuasive.

B) The previous rejection of claim 21 with respect to the antecedent basis of the limitation "or multivalent reagent according to claim 1" in the preamble has been obviated by applicant's amendment, filed 1/29/04.

C) Claims 1-21, 28 and 34-36 are indefinite in the recitation of "at least one modified monomeric non-antibody ligand V-like domain (VLD) because the metes and bounds of this phrase is ambiguous and unclear. The nature or intent of reciting "at least one" is confusing and, in turn, how this reads on the claimed compound, including the recitation of "monomeric".

D) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

Claim Rejections - 35 USC § 112 first paragraph

4. Claims 1-10, 13-21, 28, 34-37 and 40-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The following *written description* rejection is set forth herein.

Applicant's arguments, filed 1/29/04,have been fully considered but are not found convincing essentially for the reasons of record.

Applicant asserts that the basis of the rejections under 35 USC 112, first paragraph, appear based on a misunderstanding of the claimed invention, particularly with respect to the VLD.

Applicant's comments concerning the metes and bounds of VLD, relying in part on Bork et al. (Appendix G) that relates to the characteristics of immunoglobulin-like domains to help clarify the structural and functional aspects of VLDs. While Bork et al. explain that molecules with immunoglobulin-like domain can have divergent sequences from immunoglobulin molecules they can have the same secondary structure and topological characteristics. Applicant then asserts that the definition of a VLD does contain the inherent negative limitation that it not be derived from an antibody or T cell receptor and that there are

Applicant relies upon the instant specification reference to a V-like domain as being "similar" to an antibody heavy or light chain variable region because their secondary structures hare common features, including the CDR loops and 9-stranded beta-sheets. Applicant asserts that there are predictable structural motifs and consensus sequences that are common to the genus of VLDs and these are and were appreciated by the skilled artisan at the time of filing. Applicant relies upon Barclay, in part, to assert that the combination of structural similarity and sequence similarity as defined through computer analysis is necessary to define a domain type, which is consistent with the specification as filed.

In addition, applicant notes that V-like domains fo the present invention are naturally monomeric or form homodimers (see page 2, lines 26-35, page 3, lines 14-19, page 13, lines 5-7 of the instant specification).

Further, applicant acknowledges that not all non-antibody ligand comprise a VLD, but only those that do comprise a VLD are encompassed by the pending claims.

Applicant submits that the aim and benefit of the instant invention is at least two-fold: (1) the binding specificities of monomeric V-like domain binding moieties can be changed by altering the size or disulfide bonding characteristics of at least one CDR loop structure or part thereof and (2) the solubility of monomeric V-like domain binding moieties can be improved by modifying or replacing at least one CDR loop structure or part thereof.

As applicant acknowledges, applicant relies upon the Examples based upon CTLA-4 alone to support the genus of non-antibody ligand, including the myriad of modifications to CDR loop structures and parts thereof resulting in modifications to solubility because all that is required is a VLD can be modified.

Applicant submits that adequate written description and enablement exist for pending claims in that techniques for such modifications are routine molecular biology and the assays to determine whether solubility and/or binding have been affected as desired are routine biochemistry (e.g. HPLC and antibody affinity assays).

Although there may be a common topology of fold that is achieved by different sequences with respect to immunoglobulin-like domains, Bork et al. (J. Mol. Biol. 242: 309-320(1994) disclose that no single interaction or localized set of interactions can be uniquely identified as a principal determinant of the immunoglobulin-like fold, given the extreme sequence diversity (see page 318, column 2, paragraph 2). The variety of features observed in the different immunoglobulin-like domain would lead to the expectation that further subtypes and modifications of the topology (see page 318, column 2, paragraph 4). In addition, even within a one protein the different structurally similar domains have distinct binding functions (see page 318, column 1, paragraph 2). The determined crystal structures also reveal different binding modes, apparently each part of the surface of the domain can be used for interaction with other molecules (page 318, column 1, paragraph 1).

While the specification describes how to test modifications on a genus of monomeric non-antibody ligand V-like domains (VLD) to determine whether the solubility of the modified VLD is improved, it does does set forth sufficient procedures that would necessarily lead to the genus of appropriate modifications resulting in increased solubility of the genus of monomeric non-antibody ligand V-like domains (VLD). There is insufficient disclosure of detailed, relevant identifying characteristics which provides evidence that applicant in possession of the claimed invention.

As pointed out previously, the claims recite a "non-antibody ligand V-like domain (VLD)" as part of the invention.

The specification discloses on page 5 at lines 25-30 that a "V-like domain (VLD) derived from a non-antibody ligand" is any domain which has a structure *similar* to an antibody heavy or light chain variable region, and which features CDR loop structures which are surface loop structures *like* those of antibody CDRs. The bridging paragraph of pages 5-6 of the specification discloses that a "non-antibody ligand" is *any* ligand which binds a specific binding partner and which is not an antibody or T cell receptor (TcR). .

The claims are not limited to binding moieties which share a *single* "V-like domain derived from a non-antibody ligand" as a structural basis (i.e., a "scaffold") to which modifications of the loops are made to provide binding of target molecules of interest. Instead, the claims are drawn to a genus of "binding moieties" structures which comprise *any* protein domain which can be considered by ambiguous criteria to be a "V-like domain", so long as the "V-like domain" is not derived from an antibody or TcR (i.e., is "derived from a non-antibody ligand").

The genus of structures encompassed by the instant claims is large, particularly since the metes and bounds of domains that constitute a "V-like domain" are unclear and the negative limitation that the "V-like domain" not be derived from an antibody or TcR does not provide a positive description of what actually IS encompassed within the genus.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

In the instant case the specification provides binding moieties comprising a single species of monomeric V-like domain derived from a non-antibody ligand: the V domain derived from the non-antibody ligand CTLA-4. While Table 1 does suggest other sources of "V-like domains", no evidence is provided that any of the domains of any of the molecules set forth in Table 1 would function as a "binding moiety". Neither does the specification appear to describe what particular aspects of the CTLA4 V domain structure correlate with the observed function of a "binding moiety"; thus Applicant does not appear to have described a correlation between a particular structure and the claimed function that can be generalized to other "V-like domains derived from non-antibody ligands" to show that Applicant was in possession of the generic invention.

In view of the single species described which functions as a "binding moiety", the lack of an adequate description of what aspects of the structure of that single species are shared by members of the genus to provide the binding function, and the lack of clear metes and bounds of the claimed genus in view of Applicant's definitions; the specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

5. Claims 1-10, 13-21, 28, 34-37 and 40-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a binding moiety comprising the V domain of CTLA-4 in which one or more CDR loop structures has been modified or replaced with a polypeptide which has a binding affinity for a target molecule of interest, does not reasonably provide enablement for binding moieties comprising any "V-like domain from a non-antibody ligand" for the reasons of record.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments, filed 1/29/04,have been fully considered but are not found convincing essentially for the reasons of record.

Applicant asserts that the basis of the rejections under 35 USC 112, first paragraph, appear based on a misunderstanding of the claimed invention, particularly with respect to the VLD

In addition, applicant's argument's and the examiner's rebuttal are addressed above in response to applicant's comments about the rejections under 35 USC 112, first paragraph, written description and enablement.

Although there may be a common topology of fold that is achieved by different sequences with respect to immunoglobulin-like domains, Bork et al. (J. Mol. Biol. 242: 309-320(1994) disclose that no single interaction or localized set of interactions can be uniquely identified as a principal determinant of the immunoglobulin-like fold, given the extreme sequence diversity (see page 318, column 2, paragraph 2). The variety of features observed in the different immunoglobulin-like domain would lead to the expectation that further subtypes and modifications of the topology (see page 318, column 2, paragraph 4). In addition, even within a one protein the different structurally similar domains have distinct binding functions (see page 318, column 1, paragraph 2). The determined crystal structures also reveal different binding modes, apparently each part of the surface of the domain can be used for interaction with other molecules (page 318, column 1, paragraph 1).

The specification describes assays for determining whether a given non-antibody ligand possess certain desired characteristics and identifies some broad categories of compounds that might work, these description without more precise guidelines amount to little more that a starting point, a direction for further research The specification provides for a plan or an invitation for those of skill in the art to experiment practicing the claimed invention but does not provide sufficient guidance or specificity as to how to execute that plan. It provides a starting point from which one of skill in the art can perform further research in order to practice the claimed invention, but this is not adequate to constitute enablement in that will enable any person skilled in the art to make and use the invention

As pointed out previously, the scope of the instant claims encompasses a protein which can function as a "binding moiety" for any target sequence of interest and which shares at least one monomeric "V-like domain (VLD) derived from a non-antibody ligand".

The specification discloses on page 5 at lines 25-30 that a V-like domain is a domain which has a structure *similar* to an antibody heavy or light chain variable region, and which features CDR loop structures which are surface loop structures *like* those of antibody CDRs. The bridging paragraph of pages 5-6 of the specification discloses that a "non-antibody ligand" is any ligand which binds a specific binding partner and which is not an antibody or TcR. Examples of "non-antibody ligands" which provide "V-like domains" are provided in Table 1.

The claims are not limited to binding moieties which share a particular "V-like domain". Instead the claims encompass any non-antibody/non-TcR protein domain which can be broadly characterized as a "V-like domain" in which loop structures of the domain can be modified or replaced to result in affinity for a target molecule of interest, so long as certain other wished for criteria are met and the scaffold is not derived from an antibody or TcR.

As noted supra the scope of the instant claim is unclear because the definitions provided in the specification create ambiguity as to the metes and bounds of a "V-like domain derived from a non-antibody ligand".

Even were the claims limited to a V domain (as opposed to a "V-like" domain), it would still be unpredictable which V domains could be used as a scaffold to provide a binding moiety as currently recited. Although V domains do share certain basic structural features, there is variation in details of the structures that makes it unpredictable for a given V domain whether it would function as a scaffold, particularly in monomeric form, without actually testing that particular V domain.

The specification provides a single working example of a V domain that can serve as such a scaffold – the V domain of CTLA4. From results in this one working example, Applicant generalizes the observations with the CTLA4 V domain scaffold to encompass any binding domain in which a "V-like domain" is used as a scaffold. Metzler et al. (Nat. Structural Biol. 1997; 4(7):527-531) teach that the structure of CTLA-4 is distinct from that usually found in IgSF V domain in that the beta sheet surface is atypically flat (e.g. page 529). Bajorath (J. Mol. Model 1999; 5:169-170) teaches that the V domain of ICOS, one of the proteins in the same family as CTLA-4, has a non-conserved B-C loop compared to CTLA-4 (page 173), has an alternate glycosylation site in what in CTLA-4 is the ligand binding site (page 174), and in addition has other differences including loss of the A-strand conserved in other V domains (e.g., page 173). The skilled artisan would thus consider it unpredictable as to whether even a monomeric V domain from ICOS, a member of the same family as CTLA-4, could be used like CTLA-4 as a scaffold for producing a binding moiety.

The instant claims recite those characteristics observed with respect to the CTLA-4 scaffold that Applicant chose to test. However, the specification does not appear to provide guidance as to how to *predict* which other V domains or V-like domains are likely to have these recited attributes observed for the particular V domain found in CTLA4. Thus the instant claims are essentially a "wish to know" the identity of other monomeric V-like domains derived from non-antibody ligands that could function as a scaffold for insertion of target-binding sequences to form the instantly claimed "binding moiety". It has been previously decided that claims recitations so broad do not provide sufficient guidance as to how to make and use the claimed invention. See Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992). Without guidance as to which particular V domains derived from non-antibody ligands other than CTLA-to select as likely to have the desired properties of being a monomer with increased solubility relative to the wildtype and tolerant to loop substitution, it would require undue experimentation of the skilled artisan to screen V domains from any of the large number of members of the Ig superfamily which have V domains or "V-like domains" at random and hope that another besides CTLA-4 could be identified.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance as to which properties of V domains are necessary for monomer formation and tolerance to loop substitution, the identity of those particular "monomeric V-like domains derived from a non-antibody ligand" could be used to form a binding moiety as broadly as now claimed is unpredictable; thus the experimentation left to those skilled in the art, is unnecessarily, and improperly, extensive and undue.

Applicant's arguments have not been found persuasive.

6. The previous rejection of claim 28 under 35 U.S.C. 112, first paragraph, enablement with respect to the recitation of pharmaceutical composition" has been withdrawn in view of applicant's amended claim, filed 1/24/04.

However, it appears that the currently amended claim 28 is not consistent with amending the previous amended claim 28, given that the current preamble recites "a composition" but does not indicate that the previous preamble recited "a pharmaceutical composition".

Applicant is reminded the amendments are required to be compliant with 37 CFR 1.121.

Claim Rejections – 35 U.S.C. § 102

7. Claims 1, 7, 10-11, 13, 20, 21, 28, 34-37 and 40-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Peach et al. (J. Exp. Med. 1994; 180:2049-2058, IDS # AE, see entire document).

Applicant's arguments, filed 2/3/03, and arguing that the instant claims contribute a contribution over the teachings of Peach et al. have been fully considered as they apply to the instant rejection but have not been found convincing for the reasons set forth below.

Applicant's arguments, filed 1/24/04, have been fully considered but are not found convincing essentially for the reasons of record.

Applicant submit that the pending claims are novel over Peach et al. in that Peach et al. only relates to CTLA4 molecules which are fused to an immunoglobulin fragment.

Applicant argues that the prior art is based, in part, on the erroneous premise that appearance of monomers in the gel samples is related to solubility. Solubility according to the specification, solubility relates to lack of aggregation of monomers, as assessed by HPLC chromatography. Applicant argues that there is nothing in Peach et al. to suggest that monomers are more soluble than dimers nor to suggest that any of the mutant chimeric proteins behave differently with respect to aggregation. Applicant further argues that the constructs in Peach et al. are not soluble in the sense of the word as defined in the instant application, existing as discrete non-aggregate molecules in aqueous solution, in the absence of detergents or other solubilizing entities.

As pointed out previously, Peach et al. teach chimeric molecules in which complementarity determining regions (CDRs) of CD28 and CTLA4 have been exchanged (see entire document, especially Table 2). Both CTLA4 and CD28 are T cell surface proteins that are non-antibody ligands comprising at least one monomeric V-like domain. Peach et al. show in Figure 4 that chimeric proteins such as HS4, HS4A, HS7, HS8, HS10, HS11, HS12 and HS13 each exist in monomeric form. The dimeric form of each chimeric molecule is also a "multivalent reagent comprising two or more binding moieties".

Again, Peach et al. teach that the binding affinity of at least some of these chimeric proteins is altered for B7-1 compared to the parent molecules (e.g., page 2052-2053). In addition, the chimeric proteins of Peach et al. each are a "binding moiety" since they bind monoclonal antibodies to CD28 (e.g., page 2052, bridging paragraph).

Although Peach et al. is silent with respect to the effect of these changes in the CDR loop structures on solubility, Peach et al. also show in Figure 4 that chimeric proteins HS10, HS11, HS12 and HS13 each exist in monomeric form at a greater frequency than do either CD28 or CTLA4. Thus Figure 4 provides objective evidence that at least the chimeric proteins HS4, HS4-A, HS7, HS8, HS10, HS11, HS12 and HS13 have improved solubility when compared with the unmodified VLDs of CD28 and CTLA4.

With respect to applicant arguments that Peach et al. do not teach the reader to modify CDR structures within a monomeric V-like domain in order to increase the solubility of the domain, there is no requirement that the prior art appreciate the properties inherent to the product.

As pointed out previously, applicant has further argued that the binding domains taught by Peach et al. are fusion proteins, and suggests that the fused Ig constant domain is needed to achieve solubility.

The Examiner again acknowledges that the chimeric proteins are fusion proteins. However, the "comprising" language of the claims encompasses fusion proteins. Further it is noted that in Figure 4 all of the proteins, including the wildtype CD28 and CTLA4 proteins, are evaluated in fusion protein form. Thus the increase in the lower molecule weight band corresponding to monomer in the above noted constructs reflects an effect of the CDR loop modification.

Applicant has further questioned whether the lower molecular weight bands are in fact monomers, noting that the gel is of immunoprecipitated material, that the arrows marking the position of CD28Ig and CTLA4Ig monomers does not correspond to any of the lower molecular weight bands, and that Peach et al. do not describe these forms as "monomers", but rather only as "additional species".

The Examiner acknowledges that the gel of Figure 4 is of material immunoprecipitated prior to loading and that aggregates would be lost. However, the appearance of any monomer, particular relative to the level of dimer, must necessarily indicate that there was overall a shift in equilibrium towards the monomer form relative to the unmodified molecules shown in the left lanes. The Examiner further notes that the immunoprecipitation step results in both monomeric and a multivalent form (i.e., the dimeric chimeric proteins) immobilized on a solid support, as recited in claim 21.

Again, it is also acknowledged that the arrows on the left side of the gel marking the position of CD28Ig and CTLA4Ig monomers does not correspond in size with the bands that the Examiner has argued are monomeric chimeric proteins. However, on page 2052 Peach et al. point out that the chimeric proteins migrate at a position between that of CD28Ig and CTLA4Ig; thus it is not surprising that monomeric forms of the chimeric proteins should be found between the markers for monomers of CD28Ig and CTLA4Ig. It is further noted that a fair reading of the bridging paragraph on page 2052 is that Peach et al. DO consider these "additional species" to be monomers, particularly since all of the chimeric proteins migrate between the position of CD28Ig and CTLA4Ig when all proteins are subjected to SDS-PAGE under reducing conditions.

Applicant has further argued that even if the chimeric proteins of Figure 4 of Peach et al. are monomers, the teachings of Peach et al. still do not anticipate the instant claims because Peach et al. do not appreciate that modifications of the CDR loops can improve folding and/or reduce aggregation of monomeric V-like domains.

However, it is again noted that the instant claims are not a method of making and there is no requirement that Peach et al. appreciate any of the properties inherent in the molecules described. Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. In the instant case the chimeric molecules of Peach et al. appear to meet the instant claim limitations. As long as there is evidence of record establishing inherency, failure of those skilled in the art to contemporaneously recognize an inherent property, function or ingredient of a prior art reference does not preclude a finding of anticipation. Atlas Powder Co. v. IRECO, Inc., 190 F.3d 1342, 1349, 51 USPQ2d 1943, 1948 (Fed. Cir. 1999).

It is further noted that the patentability of a product does not depend on its method of production. In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See MPEP 2113. Thus claim 33 is also anticipated.

Finally, Peach et al. teach the chimeric proteins are expressed in COS cell supernatants, which since they are taken from growing cells must be considered a pharmaceutically acceptable carrier or diluent. Applicant is reminded that a "pharmaceutical composition" is claiming in terns of intended use, and the claim reads on the ingredients.

The reference teachings thus anticipate the instant claimed invention.

Applicant arguements are not found persuasive.

8. Claims 1-9, 13, 15-16, 18-19, 21, 28, 34-37 and 40-41 are rejected under 35 U.S.C. 102(e) as being anticipated by Koide (US 2003/0134386, see entire document) for the reasons of record.

Koide teaches and claims binding polypeptides which use Fn3 as a scaffold (see entire document, *including claims*).

Fn3 is a monomeric V-like domain (not found in antibodies or T cell receptors) that has "BC', "DE", and "FG" loops that correspond to CDRs1, 2 and 3 of antibodies (see especially claims 1-2 and paragraphs 97-99).

Koide teaches and claims that the Fn3 loops can be modified or replaced versus the wildtype sequence to produce a binding polypeptide that binds a target molecule of interest (e.g., claims and paragraphs 88-222 for different target molecules).

Koide teaches and claims that the loop region can vary from the wildtype FN3 loop by the insertion of from two to 25 amino acids (e.g., claim 5).

Koide teaches that the Fn3-based binding polypeptides are useful as artificial mini-antibodies whose small size and single domain structure avoid some of the problems of antibodies while allowing binding to a variety of molecular structures for therapeutic, diagnostic and catalytic applications (see especially paragraphs 1-21 ad 94-99).

Koide et al. teaches that the loops of the Fn3 domain can be replaced with loop structures derived from antibodies, including the mouse antibody D1.3(e.g., paragraphs 105-136).

Koide does not teach that the solubility of the modified Fn3 domain is improved compared to the unmodified Fn3 domain, but improvement of solubility would be inherent in at least some of the constructs of Table 1.

Similarly, although not explicitly taught, deletion of the RGD sequence of the Fn3 FG loop as taught in Table 1 would necessarily reduce the affinity of the modified loop to at least one natural ligand (e.g., the integrin □5□1, see paragraph 98)

Koide does teach that the modified Fn3 domain have a binding specificity different than the unmodified domain because binding of HEL is taught in Figures 9 and 10 for the target ubiquitin and in the Examples IX-XIII at paragraphs 171-188).

Koide also teaches replacement of a loop structure with a binding determinant from a non-antibody polypeptide since the randomized sequence inserted for the library that yielded the ubiquitin-specific domain may be considered a "non-antibody polypeptide" (see paragraphs 160-170 for libraries with non-antibody loops and paragraphs 177-180 for the production of the ubiquitin-binding polypeptide).

Labeling of the binding polypeptides with a diagnostic reagent that is a radioisotope is taught at paragraph 135. Coupling of the binding polypeptides to a solid support occurs during the panning steps of the library amplification and selection since the binding polypeptide expressed by the phage is bound to the target coupled to a dish (e.g., see paragraph 144).

Koide teaches compositions comprising the binding domains in pharmaceutically acceptable carriers such as PBS/EDTA at numerous locations (see for example paragraph 115).

It is further noted that the patentability of a product does not depend on its method of production. In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See MPEP 2113. Thus claim 33 is also anticipated.

The reference teachings thus anticipate the instant claimed invention.

9. Claims 1-21, 28 and 34-41 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

Nuttall et al. (PROTEINS: Structure, Function , and Genetics 1999; 36:217-227) creates an ambiguity regarding the contribution of Gregory Coia and Maria Galanis to the instantly claimed invention.

The Nuttall et al. paper overlaps extensively, but not completely, with respect to the teachings it provides compared to the instantly claimed invention. However, listed Inventors Coia and Galanis only appear in the acknowledgements section of the Nuttall et al. paper on page 226 as having provided "advice and helpful discussion".

Applicant was requested to clarify the contribution of each named Inventor to the instant Invention.

The Remarks indicating the contributions of the authors and inventors by applicant's representative on 1/29/04 are acknowledged.

However, it is incumbent upon the inventors named in the application, in reply to an inquiry regarding the appropriate inventorship under subsection (f) or to provide a satisfactory showing by way of affidavit under 37 CFR 1.132 that the inventorship is correct I that the reference discloses subject matter invented by the applicant rather than derived from the author or patentee notwithstanding the authorship of the article or the inventorship of the patent. See MPEP 2137.

Therefore, the rejection is maintained.

10. Claims 1 and 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koide (US 2003/0134386) in view of Bogden et al. (US Pat. No. 5,504,069).

The claims are drawn to a binding moiety comprising at least one monomeric V-like domain derived from a non-antibody ligand wherein at least one CDR loop structure or part thereof is replaced with a binding determinant derived from somatostatin.

The teachings of Koide have been discussed in full supra and teach a binding polypeptide Fn3 as a scaffold (see entire document, *including claims*). Fn3 is a monomeric V-like domain (not found in antibodies or T cell receptors) that has "BC', "DE", and "FG" loops that correspond to CDRs1, 2 and 3 of antibodies (see especially claims 1-2 and paragraphs 97-99).

Koide teaches and claims that the Fn3 loops can be modified or replaced versus the wildtype sequence to produce a binding polypeptide that binds a target molecule of interest (e.g., claims and paragraphs 88-222 for different target molecules).

Koide does not teach replacement of at least on CDR loop structure or a part thereof with a binding determinant derived from somatostatin.

However, Bogden et al. teach that somatostatin agonists were highly desirable for methods including the inhibition of trauma-induced tumor growth (see entire document). Bogden et al. teach that native somatostatin has a very short half-life in vivo because the peptide is rapidly inactivated by endo- and exopeptidases; thus agonists which maintain the function of somatostatin but remain active for longer periods were highly desirable (e.g., see column 4 at lines 35-67). Bogden et al. review that it was well known in the art at the time the invention was made that the somatostatin peptide could be modified in multiple ways to provide new structures that preserved the function of binding somatostatin receptors (see e.g., columns 5-8).

In view of the teachings of Koide that polypeptides of 2-25 amino acids can be inserted into the FG loop of FN3 to produce a binding polypeptide and the fact that somatostatin is a peptide within this size range; it would have been obvious to the ordinary artisan at the time the invention was made to insert somatostatin into the FG loop of the FN3 scaffold taught by Koide. The ordinary artisan would have been motivated to insert somatostatin into the FG loop of the Fn3 scaffold in order to provide an agonist of somatostatin function of sufficient stability and size such that it would not be readily cleaved by endo- or exopeptidases, and could therefore remain active longer in vivo than the unmodified somatostatin peptide.

In view of the teachings of Koide regarding methods of modifying the Fn3 scaffold by inserting peptides into the FG loop, and the teachings in the art with respect to the production of agonists using the somatostatin peptide sequence, the ordinary artisan at the time the invention was made would have had a reasonable expectation of producing an Fn3 scaffold having the FG loop replaced by somatostatin, and that the chimeric polypeptide would still bind somatostatin receptors. An increase in solubility compared to the unmodified Fn3 domain would be an expected outcome of inserting the longer somatostatin peptide into the FG loop. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. Claims 1 and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koide (US 2003/0134386) in view of Cai et al. (Proc. Natl. Acad. Sci. USA 1996; 93:6280-6285).

Applicant's arguments, filed 1/29/04, have been fully considered but are not found convincing essentially for the reasons of record.

In relying in part upon Bork et al. (Appendix G), applicant asserts that a skilled artisan would understand that Fn3 does not posses a V-like domain, rather it possesses a S-like domain.

However, as page 38, paragraph 4 of Bork et al. notes, there is no agreed nomenclature for most superfamilies. Also, it is not readily apparent that the recitation of the claims reflect or limited to the asserted metes and bounds or scope. For instance, it is not readily apparent that the claimed recitation and the specification as filed are consistent with the nomenclature for superfamilies, protein domains, repeats and motifs as described by Bork et al., which, in turn, is asserted and relied upon by applicant.

In addition, the claims recite "or part thereof" which opens the claims to a broader applicability of prior art.

Therefore, the art is maintained for the reasons of record, reiterated herein for applicant's convenience.

The claims are drawn to a binding moiety comprising at least one monomeric V-like domain derived from a non-antibody ligand wherein one or more CDR loop structures are replaced with one or more CDR loop structures derived from the human anti-melanoma antibody V86.

The teachings of Koide have been discussed in full supra and teach a binding polypeptide Fn3 as a scaffold (see entire document, *including claims*). Fn3 is a monomeric V-like domain (not found in antibodies or T cell receptors) that has "BC', "DE", and "FG" loops that correspond to CDRs1, 2 and 3 of antibodies (see especially claims 1-2 and paragraphs 97-99).

Koide teaches and claims that the Fn3 loops can be modified or replaced versus the wildtype sequence to produce a binding polypeptide that binds a target molecule of interest (e.g., claims and paragraphs 88-222 for different target molecules). Koide teaches that the Fn3-based binding polypeptides are useful as artificial mini-antibodies whose small size and single domain structure avoid some of the problems of antibodies while allowing binding to a variety of molecular structures for therapeutic, diagnostic and catalytic applications (see especially paragraphs 1-21 ad 94-99).

Koide et al. teaches that the loops of the Fn3 domain can be replaced with loop structures derived from antibodies, including the mouse antibody D1.3(e.g., paragraphs 105-136).

Koide does not teach replacement of one or more CDR loop structures with one or more CDR loop structures derived from the human anti-melanoma antibody V86

However, Cai et al. teach the human anti-melanoma antibody V86 (see entire document). Cai et al. teach that unlike most antibodies, the specificity of V86 is contained within the VH domain since a full VL domain is not expressed by V86 (e.g., summarized in Abstract). Cai et al. note the art-recognized applications of anti-melanoma antibodies as immunodiagnostic reagents (e.g., page 6280 introduction). Cai et al. teach the amino acid sequence of the V86 antibody (see Table 1).

In view of the teachings of Koide that CDR loops from different antibodies could be used to replace the corresponding loops of the Fn3 domain and yield a binding polypeptide with the specificity of the donor antibody; it would have been obvious to the ordinary artisan at the time the invention was made to replace the corresponding loops of the Fn3 scaffold taught by Koide with the CDRs of the V86 VH domain. The ordinary artisan would have been motivated to make such a replacement because, as taught by Koide, binding polypeptides using the Fn3 scaffold avoid certain problems associated with antibodies.

In view of the teachings of Koide regarding methods of modifying the Fn3 scaffold by replacing Fn3 loops with CDRs from an antibody, and the teachings in the art with respect to the V86 CDR sequences, the ordinary artisan at the time the invention was made would have had a reasonable expectation of producing an Fn3 scaffold having the CDRs of V86, and that the chimeric polypeptide would still bind the melanoma antigen bound by V86. An increase in solubility compared to the unmodified Fn3 domain would be an expected outcome of replacing the Fn3 loops with the V86 CDRs. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

12. No claim is allowed.

13. Applicant Note: A declaration under 37 CFR 1.131 or 1.132 would not be sufficient to overcome the rejection of the instant claims as being anticipated by or obvious over Koide (US 2003/013386). See 37 C.F.R 1.608(b).

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
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